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Lack of association between LIPC-514 C/T polymorphism of hepatic lipase and endometriosis in Iranian women

Mehdi Sahmani[1], Talaat Dabbaghi Ghaleh[2], Maryam Darabi[3], Masoud Darabi[4], Zahra Rashvand[1] and Reza Najafipour[1]

[1]*Department of Clinical Biochemistry, Cellular and Molecular Research Center, Qazvin University of Medical Sciences,* [2]*Kosar Hospital, Qazvin,* [3]*Drug Applied Research Center, Tabriz University of Medical Sciences, and* [4]*Department of Biochemistry and Clinical Laboratories, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*

Abstract

Aim: Patients with endometriosis may suffer from dyslipidemia. Hepatic lipase (HL) is involved in the metabolism of lipoproteins and has an important role in reverse cholesterol transport. The aim of this study was to investigate the association between the LIPC-514 C/T polymorphism in the HL gene and the risk of endometriosis in a group of Iranian women.

Methods: Ninety-seven patients with endometriosis and 107 women who were negative for endometriosis after diagnostic laparoscopy, as control group, were enrolled in this cross-sectional study. Samples were analyzed for polymorphism of the HL gene using polymerase chain reaction restriction fragment length polymorphism.

Results: Multivariate analysis was used to examine the association between the risk of endometriosis and LIPC-514 C/T polymorphism. There was no statistically significant difference in the frequency of the LIPC-514 C/T polymorphism between patients and the controls (60.7% CC, 34.6% CT, 4.7% TT versus 68.4%, 27.4%, 4.2%, respectively, $P = 0.52$).

Conclusion: The present study suggested that the LIPC-514 C/T polymorphism of the HL gene has no significant association with the risk of endometriosis in the studied Iranian women.

Key words: dyslipidemia, endometriosis, hepatic lipase, LIPC-514 C/T polymorphism.

Introduction

Endometriosis is a common chronic gynecologic disease that is defined as an abnormal placement of endometrial gland and stroma outside the uterus.[1] Abnormal growth of the endometrium is found mainly on the pelvic and visceral peritoneal surfaces, but also may be found on the ovaries, rectovaginal, bladder and bowel.[2] Endometriosis is associated with a spectrum of symptoms of which chronic pelvic pain is the most common. Dyspareunia, pain during menstruation and infertility are other symptoms of the disease. Laparoscopy and biopsy are the primary methods for histological diagnosis.[3,4] Endometriosis is considered a multifactorial disease and most probably a chronic inflammation in the peritoneal cavity triggers the disease.[5] Previous studies have shown that oxidative stress and inflammatory factors are involved in the pathogenesis and development of endometriosis.[6,7] A similar process exists in cardiovascular disease. Therefore, an abnormal lipid profile including increased low-density lipoprotein cholesterol (LDL-C) and

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Reprint request to: Dr Reza Najafipour, Department of Clinical Biochemistry and Genetics, Cellular and Molecular Research Center, Qazvin University of Medical Sciences, ShahidBahonar Boulevard, PO Box 34185-754, Qazvin, Iran. Email: r_najafipour@yahoo.com
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decreased high-density lipoprotein (HDL-C) and subsequently increased oxidized LDL (oxLDL) particles in peritoneal fluid could be involved in the development of endometriosis.[8–10] Hepatic lipase (HL) is a lipolytic enzyme that is synthesized and secreted by the liver.[11] It regulates plasma lipids and lipoproteins through the hydrolysis of triglycerides, LDL particle deformation and HDL catabolism.[11] HL may act as a protein ligand that facilitates the uptake of lipoproteins by cell surface receptors.[12] The hepatic lipase gene (LIPC) is located in chromosome 15q21 and is 35 kb in size with nine exons.[13] Several single nucleotide polymorphisms (SNP) were observed in the 5′-flanking region of the LIPC (–250G/A, –514C/T, –710T/C)[14,15] which has been associated with HL activity and consistently with circulating HDL-C levels.[16–18] The LIPC-514 C/T polymorphism (rs1800588) is a C to T substitution at 514 bp upstream of the transcription initiation site that is associated with low HL activity and higher plasma HDL-C levels and large LDL particles.[19,20] Melo *et al*.'s study showed that the abnormal lipid profile with elevated LDL-C and non-HDL-C may increase oxidative stress and inflammation in the peritoneal fluid of women and subsequently the risk of endometriosis.[21] Santanam *et al*. study suggests that oxLDL particles also can be involved in the development of endometriosis.[8] oxLDL induces endothelial damage and promotes the migration of leukocytes and macrophages. The release of inflammatory cytokines by these cells is followed by a platelet accumulation and formation of atherosclerotic plaques.[21] Because the LIPC-514 C/T polymorphism has been associated with dyslipidemia and increased oxLDL, this polymorphism may also be responsible for the pathogenesis of endometriosis by inducing a similar process of inflammation in the peritoneal fluid. The aim of this study was to find out the frequency of the LIPC-514 C/T polymorphism and its relationship with endometriosis risk in Iranian women with endometriosis.

Methods

Subjects

All subjects (aged 18–42 years) were selected from women referred to the Kosar Hospital (Qazvin, Iran) for diagnostic laparoscopy. The study was approved by the ethics committee of Qazvin University of Medical Sciences. A total of 97 patients had surgical and histological evidence of endometriosis, while 107 cases without the disease served as controls: uterine myoma (18 cases), dermoid cyst (20 cases), paraovarian cyst (18 cases), serous cyst (15 cases) and healthy women with infertility and/or pelvic pain (36 cases), as previously reported by us.[22] The extent of the disease was staged according to the revised American Fertility Society Classification.[23] Among the endometriosis patients, 10 patients were diagnosed with stage I, 13 patients with stage II, 35 patients with stage III and 39 patients with stage IV. None of the patients had received hormone therapy during the previous 12 months. Women were not included in the study if they had received anti-inflammatory drugs and contraceptives during the previous 3 months or if they had urological disease, endocrine disorders, familial dyslipidemia or chronic inflammation.

Assay of serum lipids

Before laparoscopy, 5 mL of peripheral fasting blood samples were obtained and subjected to centrifugation at 800 *g* for 5 min. Serum total cholesterol (TC), HDL-C and triglyceride (TG) were assessed using enzymatic methods (Selectra XL, Vitalab, the Netherlands). LDL-C was calculated using the Friedewald equation.[24] All samples were stored at –70°C for later simultaneous measurement.

Genomic DNA analysis

Genomic DNA was extracted from the leukocytes in blood samples using a DNA purification kit (Qiagen, USA). A 285-bp sequence of the LIPC was amplified by polymerase chain reaction (PCR) in a DNA thermal cycler (ABI, Veriti, USA) by using oligonucleotide primers, forward 5′-TCTAGGATCACCTCTCAATGG GTCA-3′ and reverse 5′-GGTGGCTTCCACGTGG-CTGCCTAAG-3′.

The PCR condition were 95°C for 3 min, 35 cycles of 95°C for 60 s, 63°C for 30 s, 72°C for 30 s followed by 72°C for 7 min.[25] Restriction digestion of the PCR product with the N*la*III enzyme results in fragments of 215 and 70 bp in rare homozygotes, 285, 215 and 70 bp in heterozygotes, and 285 bp in common homozygotes.

Statistical analysis

Values were presented as the mean ± standard deviation, and statistical significance was defined as $P < 0.05$. Student's *t*-test and χ^2-test were used to compare variables between the two groups. Statistically significant differences in means between genotypes were assessed by ANOVA. Logistic regression analyses were performed for evaluating genotype distribution with respect to the presence of endometriosis as a

Table 1 Metabolic parameters of patients with endometriosis versus control

	Control ($n = 107$)	Endometriosis ($n = 97$)	*P*
Age, years	29.5 ± 5.5	29.8 ± 5.4	0.66
Body mass index, kg/m^2	26.9 ± 3.9	25.1 ± 3.3	0.001
Waist, cm	81.2 ± 9.7	80.6 ± 9.1	0.69
Cholesterol, mg/dL	175 ± 30	216 ± 38	<0.001
Triglyceride, mg/dL	127 ± 47	128 ± 48	0.86
HDL-C, mg/dL	40 ± 9	46 ± 10	<0.001
LDL-C, mg/dL	101 ± 20	130 ± 22	<0.001

Values are mean ± standard deviation. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2 LIPC-514 C/T genotype distributions in patients with endometriosis versus control

Gene	Control ($n = 107$)	Endometriosis ($n = 95$)	*P*
CC	65 (60.7%)	65 (68.4%)	0.52
CT	37 (34.6%)	26 (27.4%)	
TT	5 (4.7%)	4 (4.2%)	

P-values: χ^2-tests.

Table 3 Logistic regression analysis of LIPC-514 C/T alleles with respect to the presence of endometriosis as dependent variable

	Univariate			Multivariate†		
	OR	95% CI	*P*	OR	95% CI	*P*
LIPC-514 T	0.71	0.40–1.28	0.26	0.64	0.30–1.35	0.24

Values are 95% confidence interval (95% CI) and odds ratio (OR). †Adjusted for body mass index, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol.

dependent variable. All analyses were carried out using SPSS ver. 11.0 for Windows (SPSS, Chicago, IL, USA).

Results

Demographic and metabolic parameters of patients and controls are shown in Table 1. Women with endometriosis had lower body mass index (BMI) values than the controls (25.1 ± 3.3 vs 26.9 ± 3.9, $P = 0.001$). The TC level of the endometriosis group was higher than the control group (216 ± 38 vs 175 ± 30 mg/dL, $P < 0.001$) as well as the level of LDL-C (130 ± 22 vs 101 ± 20 mg/dL, $P < 0.001$) and HDL-C (46 ± 10 vs 40 ± 9 mg/dL, $P < 0.001$). TG levels were higher in the endometriosis group but this difference was not statistically significant between the two groups (128 ± 48 mg/dL vs 127 ± 47 mg/dL, $P = 0.86$). The genotype distribution of the HL-514 C/T polymorphism of both groups were in the Hardy–Weinberg equilibrium (both $P > 0.05$). The distribution of genotypes was not different between the endometriosis group and the control group (68.4% CC, 27.4% CT, 4.2% TT vs 60.7%, 34.6%, 4.7%, respectively, $P = 0.52$) (Table 2). The risk of endometriosis in different genetic groups was calculated by logistic regression analysis (Table 3). This analysis showed no statistically significant differences between groups in the risk of endometriosis ($P = 0.24$, odds ratio [OR] = 0.64, 95% confidence interval [CI] = 0.30–1.35), after adjustment for BMI, HDL-C and LDL-C. In further analyses, we found also no association between the LIPC-514 C/T SNP and the four stages of endometriosis. ANOVA analysis also showed no statistically significant differences in metabolic parameters in the studied women (Table 4). There was no difference even when the control and endometriosis groups were analyzed separately.

Table 4 Metabolic parameter according to genotypes

	LIPC-514 C/T			
	CC	CT	TT	*P*
n	130	63	9	
Age, years	29.9 ± 5.0	29.1 ± 5.3	30.4 ± 6.7	0.56
Body mass index, kg/m^2	26.2 ± 4.2	25.7 ± 2.9	26.0 ± 2.8	0.69
Waist, cm	81.0 ± 9.7	80.5 ± 9.1	82.1 ± 8.8	0.87
Cholesterol, mg/dL	196 ± 42	193 ± 37	189 ± 34	0.80
Triglyceride, mg/dL	131 ± 48	123 ± 48	114 ± 39	0.41
HDL-C, mg/dL	43 ± 9	44 ± 12	41 ± 6	0.66
LDL-C, mg/dL	115 ± 28	112 ± 21	114 ± 25	0.73

Values are means ± standard deviation, ANOVA. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Discussion

The purpose of this study was to test the potential association of the LIPC-514 C/T polymorphism with the risk of endometriosis in a population of Iranian women. Endometriosis is characterized by an inflammatory reaction in the peritoneal cavity.[5,26] Ploak *et al*. study showed an increased oxLDL levels in the peritoneal fluid of women with advanced stages of endometriosis.[27] High LDL-C levels may be a factor that stimulates cell proliferation processes in the arterial vessels and can initiate atherosclerosis.[9,28] The present study demonstrated that patients with endometriosis had lower BMI and higher HDL-C than the control group. These observations are consistent with previous studies[21,29,30] and have been discussed earlier.[22] In this study, patients with endometriosis had significantly higher levels of TC and LDL-C than patients without endometriosis, but no significant difference was found for TG, which might be attributed to the lower BMI in the endometriosis group. Previous studies have reported that BMI is a major contributor of TG levels.[31]

Hepatic lipase has a key role in the metabolism of plasma lipoproteins and is involved in reverse cholesterol transport.[12,32] Human studies have shown that HL activity tends to be increased in the presence of smoking, insulin resistance in type II diabetes mellitus and females with increased omental fat mass, so these reports suggests that HL may be a proatherogenic factor.[33–35] HL also promotes the formation of small and dense atherogenic LDL particles.[8] The LIPC-514 C/T polymorphism was first reported to be associated with the reduced HL activity in men with coronary heart disease (CHD).[18] Several studies have also reported the relationship between this polymorphism and the risk of CHD in a different population.[36–38] Yamazaki *et al*.'s study suggested that in familial combined hyperlipidemia, the LIPC-514 T allele led to increase in malondialdehyde-modified LDL, a species of oxLDL, which may be a useful biomarker for atherosclerosis.[39] Issacs *et al*.'s study showed that the T allele of the –514 C/T polymorphism in the promoter region of the LIPC is associated with elevation of HDL-C levels.[40] Our study demonstrated no significant difference in HDL-C levels in individuals with the TT compared with the CC genotype, which is inconsistent with some previous studies.[30] HDL-C levels depend on various factors such as environment, diet, exercise and genetics. In other words, the results of this study indicate that the T allele alone is not the determinant of plasma HDL-C levels. Previous findings on the effect of the LIPC-514 C/T polymorphism on the risk of myocardial infarction (MI) seems to be inconsistent with our results. Other studies found either no association[41,42] or a protective effect.[43,44] We observed that the genotype distributions and allele frequency of the LIPC-514 C/T polymorphism were not significantly different between the individuals with and without endometriosis and between the different stages of endometriosis. There is ethnic heterogeneity in the LIPC-514 C/T genotype distribution in healthy populations across the world. In the present study, the frequency of the LIPC-514 promoter T allele in females is similar to the frequencies previously reported in Caucasian subjects, but lower than those in Japanese.[45,46]

In this study, no significant association between LIPC-514 C/T genotype and endometriosis was observed, but due to the small sample size of the population examined, further research involving a larger number of patients is needed. A recent genome-wide association study conducted on endometriosis identified few risk loci with OR for the association of less than 1.5.[47] So, consistent with our findings, it is unlikely

that a hypothetical association between the LIPC-514 C/T SNP and endometriosis would result in an OR of more than 1.5. The main limitation of the present study was no standardization of the intensity of patients' physical activity, a factor that may also influence the levels of serum lipids. Physical activity level can be assessed by self-report methods such as questionnaires and activity diaries.[48]

To the best of our knowledge, this is the first study to look for an association between the LIPC-514 C/T polymorphism of HL and the risk of developing endometriosis. Our results showed that the LIPC-514 C/T polymorphism is not associated with endometriosis risk in a population of Iranian women. Further studies are necessary to explain the role of LIPC in the pathogenesis of endometriosis as well as to characterize the relationship of the LIPC-514 C/T polymorphism with endometriosis susceptibility.

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References

1. Donnez J, Squifflet J, Pirard C, Jadoul P, Wyns C, Smets M. The efficacy of medical and surgical treatment of endometriosis-associated infertility and pelvic pain. *Gynecol Obstet Invest* 2002; **54** (Suppl 1): 2–7; discussion 7–10.
2. Giudice LC, Kao LC. Endometriosis. *Lancet* 2004; **364**: 1789–1799.
3. Kennedy S, Bergqvist A, Chapron C *et al*. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005; **20**: 2698–2704.
4. Marchino GL, Gennarelli G, Enria R, Bongioanni F, Lipari G, Massobrio M. Laparoscopic visualization with histologic confirmation represents the best available option to date in the diagnosis of endometriosis. *Fertil Steril* 2005; **84**: 38.
5. Ulukus M, Ulukus EC, Seval Y, Zheng W, Arici A. Immunology of endometriosis. *Minerva Gynecol* 2005; **7**: 237–248.
6. Van Langendonckt A, Casanas-Roux F, Dolmans MM, Donnez J. Oxidative stress and peritoneal endometriosis. *Fertil Steril* 2002; **77**: 861–870.
7. Jackson LW, Schisterman EF, Dey-Rao R, Browne R, Armstrong D. Oxidative stress and endometriosis. *Hum Reprod* 2005; **20**: 2014–2020.
8. Santanam N, Song M, Rong R, Murphy AA, Parthasarathy S. Atherosclerosis, oxidation and endometriosis. *Free Radic Res* 2002; **36**: 1315–1321.
9. Linton MF, Fazio S. Class A scavenger receptors, macrophages, and atherosclerosis. *Curr Opin Lipidol* 2001; **12**: 489–495.
10. de Villiers WJ, Smart EJ. Macrophage scavenger receptors and foam cell formation. *J Leukoc Biol* 1999; **66**: 740–746.
11. Bensadoun A, Berryman DE. Genetics and molecular biology of hepatic lipase. *Cur Opin Lipidol* 1996; **7**: 77–81.
12. Tall AR. An overview of reverse cholesterol transport. *Eur Heart J* 1998; **19**: A31–A33.
13. Carr MC, Brunzell JD, Deeb SS. Ethnic differences in hepatic lipase and HDL in Japanese, black, and white Americans: Role of central obesity and LIPC polymorphisms. *J Lipid Res* 2004; **45**: 466–473.
14. Freeman DJ, Griffin BA, Holmes AP *et al*. Regulation of plasma HDL cholesterol and subfraction distribution by genetic and environmental factors: Associations between the *Taq*I B RFLP in the CETP gene and smoking and obesity. *Arterioscler Thromb* 1994; **14**: 336–344.
15. Bamberger M, Lund-Katz S, Phillips MC, Rothblat GH. Mechanism of the hepatic lipase induced accumulation of high-density lipoprotein cholesterol by cells in culture. *Biochemistry* 1985; **24**: 3693–3701.
16. Jansen H, Verhoeven AJ, Weeks L *et al*. A common C-to-T substitution at position 2480 of the hepatic lipase promoter associated with a lowered lipase activity in coronary artery disease patients. *Arterioscler Thromb Vasc Biol* 1997; **17**: 2837–2842.
17. Guerra R, Wang J, Grundy SM, Cohen JC. A hepatic lipase (LIPC) allele associated with high plasma concentrations of high density lipoprotein cholesterol. *Proc Natl Acad Sci U S A* 1997; **94**: 4532–4537.
18. Zambon A, Deeb SS, Hokanson JE, Brown BG, Brunzell JD. Common variants in the promoter of the hepatic lipase gene are associated with lower levels of hepatic lipase activity, buoyant LDL, and higher HDL2 cholesterol. *Arterioscler Thromb Vasc Biol* 1998; **18**: 1723–1729.
19. Kashani Farid MA, Azizi F, Hedayati M, Daneshpour MS, Shamshiri AR, Siassi F. Association between CETP Taq1B and LIPC -514C/T pol-ymorphisms with the serum lipid levels in a group of Tehran's population: A cross sectional study. *Lipids Health Dis* 2010; **9**: 96–103.
20. Molly CC, John DB. Ethnic differences in hepatic lipase and HDL in Japanese, black, and white Americans: Role of central obesity and LIPC polymorphisms. *J Lipid Res* 2004; **45**: 466–473.
21. Melo AS, Silva J, Silva R, Poli-Neto O, Ferriani R, Vieira C. Unfavorable lipid profile in women with endometriosis. *Fertil Steril* 2010; **93**: 2433–2436.
22. Sahmani M, Ghaleh TD, Darabi M, Darabi M, Rashvand Z, Najafipour R. The I405V polymorphism of CETP gene and lipid profile in women with endometriosis. *Gynecol Endocrinol* 2013; **29**: 712–715.
23. The Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility. *Fertil Steril* 2006; **86**: S156–S160.
24. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499–502.
25. Couture P, James D, Otvos L *et al*. Ordovas association of the C2514T polymorphism in the hepatic lipase gene with variations in lipoprotein subclass profiles the framingham offspring study. *Arterioscler Thromb Vasc Biol* 2000; **20**: 815–822.
26. Olive DL, Schwartz LB. Endometriosis. *N Engl J Med* 1993; **328**: 1759–1769.

27. Polak G, Koziol-Montewka M, Gogacz M, Blaszkowska I, Kotarski J. Increased oxidized LDL cholesterol levels in peritoneal fluid of women with advanced-stage endometriosis. *Ginekol Pol* 2011; **82**: 191–194.
28. Schulze PC, Lee RT. Oxidative stress and atherosclerosis. *Curr Atheroscler Rep* 2005; **7**: 242–248.
29. Hediger ML, Hartnett HJ, Louis GM. Association of endometriosis with body size and figure. *Fertil Steril* 2005; **84**: 1366–1374.
30. Verit FF, Erel O, Celik N. Serum paraoxonase-1 activity in women with endometriosis and its relationship with the stage of the disease. *Hum Reprod* 2008; **23**: 100–104.
31. Schubert CM, Rogers NL, Remsberg KE *et al*. Lipids, lipoproteins, lifestyle, adiposity and fat-free mass during middle age: The Fels Longitudinal Study. *Int J Obes (Lond)* 2006; **30**: 251–260.
32. Takata M, Inazu A, Katsuda S *et al*. *CETP* (cholesteryl ester transfer protein) promoter –1337 C>T polymorphism protects against coronary atherosclerosis in Japanese patients with heterozygous familial hypercholesterolaemia. *Clin Sci* 2006; **111**: 325–331.
33. Kong C, Nimmo L, Elatrozy T *et al*. Smoking is associated with increased hepatic lipase activity, insulin resistance, dyslipidaemia and early atherosclerosis in Type 2 diabetes. *Atherosclerosis* 2001; **156**: 373–378.
34. Baynes C, Henderson AD, Anyaoku V *et al*. The role of insulin insensitivity and hepatic lipase in the dyslipidaemia of type 2 diabetes. *Diabetic Med* 1991; **8**: 560–566.
35. Carr MC, Hokanson JE, Zambon A *et al*. The contribution of intraabdominal fat to gender differences in hepatic lipase activity and low/high density lipoprotein eterogeneity. *J Clin Endocrinol Metab* 2001; **86**: 2831–2837.
36. Wang HR, Jiang M, Qiu JP. Quantitative assessment of the effect of hepatic lipase gene polymorphism on the risk of coronary heart disease. *Arch Med Res* 2010; **41**: 383–390.
37. Zhang C, Lopez-Ridaura R, Rimm EB. Genetic variation in the hepatic lipase gene and the risk of coronary heart disease among US diabetic men: Potential interaction with obesity. *Diabetologia* 2006; **49**: 1552–1559.
38. Ghatrehsamani K, Darabi M, Rahbani M, Hashemzadeh Chaleshtory M, Farrokhi E, Noori M. Combined hepatic lipase -514C/T and cholesteryl ester transfer protein I405V polymorphisms are associated with the risk of coronary artery disease. *Genet Test Mol Biomarkers* 2009; **13**: 809–815.
39. Yamazaki K, Bujo H, Taira K *et al*. Increased circulating malondialdehyde-modified LDL in the patients with familial combined hyperlipidemia and its relation with the hepatic lipase activity. *Atherosclerosis* 2004; **172**: 181–187.
40. Isaacs A, Sayed-Tabatabaei FA, Hofman A *et al*. The cholesteryl ester transfer protein I405V polymorphism is associated with increased high-density lipoprotein levels and decreased risk of myocardial infarction: The Rotterdam Study. *Eur J Cardiovasc Prev Rehabil* 2007; **14**: 419–421.
41. Tobin MD, Braund PS, Burton PR *et al*. Genotypes and haplotypes predisposing to myocardial infarction: A multilocus case-control study. *Eur Heart J* 2004; **25**: 459–467.
42. Fan YM, Salonen JT, Koivu TA *et al*. Hepatic lipase C-480T polymorphism modifies the effect of HDL cholesterol on the risk of acute myocardial infarction in men: A prospective population based study. *J Med Genet* 2004; **41**: e28.
43. McCaskie PA, Cadby G, Hung J *et al*. The C-480T hepatic lipase polymorphism is associated with HDL-C but not with risk of coronary heart disease. *Clin Genet* 2006; **70**: 114–121.
44. Fan YM, Lehtimaki T, Rontu R *et al*. Age-dependent association between hepatic lipase gene C-480T polymorphism and the risk of pre-hospital sudden cardiac death: The Helsinki Sudden Death Study. *Atherosclerosis* 2007; **192**: 421–427.
45. Inazu A, Nishimura Y, Terada Y, Mabuchi H. Effects of hepatic lipase gene promoter nucleotide variations on serum HDL cholesterol concentration in the general Japanese population. *J Hum Genet* 2001; **46**: 172–177.
46. Carr MC, Brunzell JD, Deeb SS. Ethnic differences in hepatic lipase and HDL in Japanese, black,and white Americans: Role of central obesity and LIPC polymorphisms. *J Lipid Res* 2004; **45**: 466–473.
47. Albertsen HM, Chettier R, Farrington P, Ward K. Genome-wide association study link novel Loci to endometriosis. *PLoS ONE* 2013; **8**: e58257.
48. Aadahl M, Jørgensen T. Validation of a new self-report instrument for measuring physical activity. *Med Sci Sports Exerc* 2003; **35**: 1196–1202.